Remarks

Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, and 43-65 were pending in the subject application. By this Amendment, claims 1-4, 6-8, 43, 45-48, and 50 have been amended, claim 51 has been cancelled, and new claims 66-68 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, 43-50, and 52-68 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

Support for the amendments to claims 1 and 43, and new claims 67 and 68, can be found, for example, at page 25, lines 10-15, of the specification as filed. Support for new claim 66 can be found, for example, at page 6, lines 12-14, of the specification as filed. Support for the amendments to claims 2-4, 6-8, 45-48, and 50 can be found throughout the specification and claims as filed.

The applicants gratefully acknowledge the Examiner's indication that claims 46, 48, and 51 have been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form. By this Amendment, dependent claim 51, which recites that the administering results in reduced IgE levels and increased IgG2a levels within the patient, has been cancelled. Independent claims 1 and 43 have been amended to recite that the administering results in reduced IgE levels and increased IgG2a levels. Accordingly, in view of the allowability of claim 51, the applicants respectfully submit that claims 1 and 43 as amended, and claims that depend from claims 1 and 43, are allowable.

Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 43-45, 47, 49, 50, 52, and 53-65 have been rejected under 35 U.S.C. §103(a) as being obvious over Hogan *et al.* (*Eur. J. Immunol.*, 1998, 28:413-423), in view of Li *et al.* (*J. Immunol.*, 1996, 157:3216-3219), Dow *et al.* (U.S. Patent No. 6,693,086), and O'Donnell *et al.* (*J. Immunol.*, 1999, 163:4246-4252). The applicants respectfully traverse.

The specification teaches, and claims 1 and 43 recite, that administration of the nucleic acid sequences encoding IL-12 and IFN-γ effectively increases Th1-type cytokine production and decreases Th2-type cytokine production. The references cited in the Office Action provide no reasonable expectation of achieving this result.

The Office Action indicates that the O'Donnell *et al.* publication supplements the other cited references. O'Donnell *et al.* investigated the role of IL-12 in the Bacillus Calmette-Guerin (BCG)-mediated immune response, and whether such an immune response could be enhanced by supplementation of exogenous rIL-12. The O'Donnell *et al.* publication observes that intravesical co-administration of BCG plus rIL-12 augments urinary IFN-γ production more strongly than either single agent alone, providing an immunological basis for using exogenous IL-12 in conjunction with BCG for bladder cancer immunotherapy. The observed increase in IFN-γ production upon co-administration of IL-12 and antigen does not provide a reasonable expectation of success in increasing Th1-type cytokine production and decreasing Th2-type cytokine production by administering nucleic acid sequences encoding IL-12 and IFN-γ.

Moreover, as indicated at page 30, lines 3-4, of the subject specification, and as shown in Figure 3C, administration of plasmids encoding IL-12 and IFN-γ resulted in a synergistic shift in cytokine profile. The applicants respectfully submit that there is nothing in the O'Donnell *et al.* publication or the other cited references to suggest that administration of a nucleic acid sequence encoding IL-12 and a nucleic acid sequence encoding IFN-γ would have a synergistic effect. A Declaration under 37 C.F.R. §1.132 by Dr. Shyam Mohapatra was submitted with the applicants' previous Amendment. Dr. Mohapatra explains in his Declaration that, "while it is true that IL-12 and IFN-γ have complex interactions and regulatory roles, this does not mean that delivery of nucleic acids encoding these two cytokines is more likely to have a synergistic effect, and synergy certainly would not be expected by one of ordinary skill in the art." Figure 3C is a graph showing an analysis of the dominant cytokine pattern after cytokine DNA vaccination in a mouse model. To examine the

dominant pattern of cytokine responses, IFN-γ/IL-4 and IL-2/IL-4 ratios were compared among different groups of mice. The results indicate that the net cytokine balance shifted in favor of the Th1-type response in cytokine-vaccinated mice; however, this shift was significantly greater in the group vaccinated with the combination of IFN-γ and IL-12. Moreover, Figure 3C shows that the ratio of IFN-γ /IL-4 was increased beyond what would be expected from the additive effects of IL-12 and IFN-γ, individually. As indicated by Dr. Mohapatra, the benefits of the claimed method and compositions are unexpected in view of the cited references, and have a significant, practical advantage for immunotherapy.

As indicated above, the applicants have amended claims 1 and 43 to recite that administration of the nucleic acid sequences resulted in reduced IgE levels and increased IgG2a levels. Likewise, dependent claims 67 and 68 have been added, which recite that the pharmaceutical composition increases Th1-type cytokine production, increases IgG2a, decreases Th2-type cytokine production, and reduces serum IgE *in vivo*. The applicants respect submit that claims 1 and 43 as currently amended, and claims 67 and 68 are commensurate in scope with the unexpected results.

Hogan *et al.* showed that the effectiveness of IL-12 was dependent upon the presence of IFN-γ gene expression. The Hogan *et al.* publication describes a single experiment showing that vaccinia virus-mediated delivery and expression of the IL-12 gene significantly decreased the number of BAL eosinophils only if mice had the IFN-γ gene. As explained by Dr. Mohapatra in his Declaration, one of ordinary skill in the art would conclude that to exert its effect on eosinophilia, IL-12 requires the IFN-γ gene to be present and that IL-12 presumably acts by inducing IFN-γ gene expression. One of ordinary skill in the art would not interpret these results to demonstrate or suggest that exogenous delivery of IL-12 and IFN-γ genes together provide a synergistic effect. (paragraph 6, page 4, Mohapatra Declaration)

When the inventors of the subject invention administered both plasmids together at half of the dosage (50 micrograms of each cytokine-encoding plasmid per mouse), a synergistic effect was observed (shown in Figure 3C). As explained by Dr. Mohapatra,

> From the previous data, we would have reasonably expected a result similar to that of either IL-12 or IFN-gamma administered individually. Thus, at the time the application was filed, based on all previous reports, one of ordinary skill in the art would expect that administering the combination of IL-12 and IFN-gamma-encoding plasmids at half amounts (50 micrograms each per mouse) would yield effects similar

> to that of IL-12 or IFN-gamma alone. Also, neither an additive nor a synergistic effect would be expected or reasonably predicted from the combination of IL-12 and IFN-gamma-encoding plasmids at 100 micrograms per mouse, because doubling the dose could easily lead to toxicity. (paragraph 6, pages 4-5, Mohapatra Declaration)

It is well settled in patent law that a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness. Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). The benefits of the claimed method and compositions are unexpected in view of the cited references, and have a significant, practical advantage for immunotherapy. Therefore, the applicants respectfully submit that the claimed invention is not obvious over the prior art.

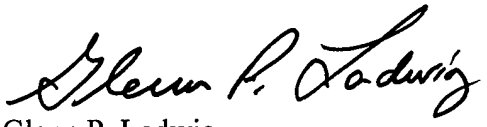
In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Glenn P. Ladwig
Patent Attorney
Registration No. 46,853
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

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Amendment Transmittal Letter
Supplemental Information Disclosure Statement, Form PTO/SB/08, and references